REMARKS/ARGUMENTS

This is in response to the Office Action of May 6, 20004 and the Notice of February 7, 2005. The helpful telephone comments of Examiner DiBrino regarding the format of the present Amendment and Response are appreciated. The present Amendment and Response assumes that the Amendment of 11/4/04 has been entered. This is consistent with the fact that the Amendment of 11/4/04 appears in PAIR. **The Amendments to the Specification made by Amendment dated 11/4/04 are therefore considered entered and not repeated here.** In order to clarify matters of form relating to amendments of commas in the claims, the claim set existing as of 11/4/04 is now presented as new claims 49-59. With regard to the amendment of 11/4/04 being directed to a non-elected invention, the newly presented claims 49-59 track claims 37 and 39-48, but do not contain the language referring to a T cell receptor which was added 11/4/04 and which was objected to in the Notice of February 7, 2005. The Arguments/Remarks of the 11/4/04 Amendment are substantially repeated herein.

The non-final Office Action dated 05/06/2004 rejected claims 8, 9, 37-40, 42, 44, and 46. Claims 41, 43 and 45 were withdrawn from consideration.

In view of the above amendments and the following remarks, the Examiner is respectfully requested to allow claims 49-59 and pass this application to issue.

A sincere effort has been made to avoid most of the rejections. The objections to the specification have been avoided, except for not changing the nature of the continuation. The court has been quite clear that it is the nature of the application and not the designation given by the applicant that decides whether an application is a continuation or continuation-in-part. Therefore, there is no need for applicant to define which is relevant as the court will decide regardless of what the applicant states. The Examiner is respectfully requested to withdraw this objection.

Claims 37 and 47 are now presented as claims 49 and 58 and exclude the non-elected invention relating to T-cell receptors. Claim 38 has been omitted without prejudice to renewal.

Support for the amendments to claim previous 37 (now claim 49) and for new claim 59 are found on page 35, lines 9 – 17. Support for new claim 58 is found in original claims 37 and 46.

The primary issue is scope. The Examiner is familiar with this invention having been involved in the prosecution of parent applications. That applicants have made a major contribution to the scientific literature cannot be gainsaid. Prior to applicants' discovery it was not known that there was an internalization sequence associated with type-2 and other receptors that was involved in the dimerization of such receptors and their activation and internalization. Prior to the subject invention the algorithm for identifying such sequences was unknown. Prior to the subject invention the use of the internalization sequence as a substitute for the second receptor was not known, nor was it known that an oligopeptide could activate such receptors in the absence of the ligand for such receptors. Prior to the subject invention, it was not known that small molecules could be used to mimic the internalization sequence of the receptors.

The fact that small molecules, including synthetic molecules, can be used is well established as evidenced by WO 04/05323. The compounds described and claimed in that application were discovered following the teachings of the subject invention. All of the disclosed compounds can be used in screening for other compounds and can serve as agonists or antagonists. Thus, the subject teaching is no chimera. Rather, the indicated application does provide evidence that the compounds are available and that by a suitable screening technique taught by the subject application, compounds that fulfill the subject claims are available.

Furthermore, applicants are not claiming compounds *per se*. Applicants are only claiming a method for modulating the activity of a receptor. For the most part, the

disclosed receptors are type-2 receptors. On pages 42 – 44, numerous receptors and their internalizing peptides are described. The experimental section exemplifies a large number of receptors and the effect of their complementary internalizing sequence. Antibodies and oligopeptides have been shown to be active in this and other applications. The indicated PCT application demonstrates that the internalizing sequence of the EPO receptor is responsive to a wide variety of small organic compounds. Therefore, following the procedures set forth in the subject application, one may expect with substantial certainty to obtain compounds that will modulate the activity of one of the receptors coming within the class defined by the claims.

The present claims have defined substantial structural limits for the compounds included within its scope. The molecular weight of the compounds is narrowly restricted to between 100 and 2,500 daltons. The compounds must have a cyclic structure and defined substituents. While a large number of compounds are included within the scope of the subject claims, the number of compounds is not undue and no undue experimentation is required to identify compounds that fulfill the requirements of the claims. What has happened to the rights of a pioneer inventor? Certainly, this is a pioneer invention. As indicated above, no one appreciated the opportunity available for developing compounds that could modulate the activity of type-2 receptors at other than the ligand binding site. Nothing is being taken away from the public that the public had prior to the subject invention. Unaware of the opportunity to modulate receptor activity by using small molecules that bind at the internalization site, the public was enlightened by the subject work as to the opportunity.

Furthermore, it is well known that there is a great reluctance to try small molecules that must compete with the binding of two proteins. The number of potential contacts between a small molecule and a protein is far inferior to the number of contacts between two proteins. In this situation, there is substantial uncertainty whether a small molecule will suffice. However, the subject inventors pioneered and persevered in trying small oligopeptides and were rewarded for their efforts. The small oligopeptides worked! Following that experience, small synthetic molecules were screened and found to be

effective as evidenced by the disclosure in WO 04/05323. It is not known what more should be required to support the scope of the present claims.

In the Office Action dated 05/06/04 it is stated on page 4 that the claims encompass any exogenous compound and there is insufficient disclosure in the specification of a method of using the exogenous compound. It is submitted that this statement flies in the face of the extensive specification where it is taught and exemplified how to use the subject compounds, using oligopeptides as paradigmatic. In the experimental section it is shown that with cells in culture one can modulate the activity of a wide variety of type-2 receptors. Quite obviously, this ability can be used to determine the effect of the activation of the receptor on the pathways in the cell, the effect of drugs in modulating such pathways and by using conventional methods, the utility of compounds as agonists and antagonists for the receptors for therapeutic purposes.

On page 5 the Examiner calculates the possibility of their being 14^{20} possible oligopeptides encompassed by the claims. This number is submitted to be ingenuous. Patent applications are written to those of skill in the art. Anyone of skill in the art would determine the essential amino acids for binding and could then modify others appropriately. The Examiner is well aware of the ability to perform glycine or leucine walks to identify essential amino acids for binding. Once such walks are accomplished, which can be done with little effort, if one wished other than the essential amino acids could be modified. Applicants should not be denied reasonable scope, when the scope is not as dire as the Examiner suggests. Rather those of skill in the art would know how to make changes in the oligopeptides to maintain and possibly enhance activity, if such was desired.

On the same page, the Examiner indicates that there must be some direction as to the nature of the exogenous compounds. It is submitted that applicants have provided such direction in the claims in light of the nature of the invention. Broad inventions should be claimed broadly. This invention is a very broad invention. Applicants should not be limited to a narrow scope of claims that are restricted to being a tool, while others enjoy the fruits of applicants' discovery. The further reduction in scope would eviscerate the claims

to where they were of little value to applicants and of great value to others. Rather, applicants who have developed a pioneering invention should be granted claims that correspond to their contribution to the art. If among the reasons for granting patents is the disclosure of the invention to the public, so that the public may enjoy the invention when the patent has expired, then applicants should be granted reasonable scope to allow them to exploit their invention reasonably.

What the Examiner would wish is that applicants be limited to specific structures that have been found to be successful in modulating the activity of the different receptors. It would be better for inventors of inventions such as this one to retain them as trade secrets, since the inventors will not receive much benefit from disclosing their inventions in patent applications. Rather they will alert the interested public to the opportunity and create a race to the patent office for individual compounds or genera. This cannot be the intent of the patent law. The rejection depends upon what "possession" means. If possession means a structure with a specific formula, then applicants disclosed oligopeptides and the prior art disclosed antibodies as effective. This is much more than an outline of what an exogenous compound is. Rules that were developed in the absence of the tools available today should not be applied as if nothing has occurred in the interim to allow persons of skill in the art to determine exogenous compounds. Considering the pioneering nature of the subject invention some latitude should be given as to the extent of the definition of the structure that needs to be defined under the Examiner's strictures.

In view of the above arguments, applicants traverse the rejection as to claims 37-40, 42, 44 and 46 and if appropriate as to newly submitted claims 47 and 48. (now claims 58-59). So far as the therapeutic aspect of the exogenous compounds, applicants need not have a demonstration for every possible utility coming within the scope of the claim. Applicants have *in vitro* demonstrations of the activity of their compounds. Compounds that can be effective therapeutically can be readily determined by using the subject disclosure.

Regarding Office Action (dated 05/06/04) Paragraph 8, the issue of priority as appropriate will be discussed in the succeeding paragraphs.

Regarding Office Action (dated 05/06/04) Paragraph 10, claims 8 and 9 have been cancelled and the rejection avoided. As to claim 46 (now 57), the amendment to claim 37 (now claim 49) avoids the rejection. There is no need to discuss the right to priority as to these claims.

Regarding Office Action (dated 05/06/04) Paragraph 11, for the reasons given in paragraph 10, the rejection is avoided.

Regarding Office Action (dated 05/06/04) Paragraph 12, the rejection has been avoided by amendment. The language finds support in claim 37 and the U.S. analog is reported on page 3, line 19 and incorporated by reference.

Regarding Office Action (dated 05/06/04) Paragraph 13, the rejection has been avoided by amendment. It is clear from the reference that it was believed that it was the MHC sequence that was active. This was based on the erroneous premise that the receptor when bound to its ligand would bind to an MHC molecule and be endocytosed. As evidenced by the subject invention, it is a second molecule of the receptor that binds, not an MHC molecule. Without the present disclosure, one would have been led down an unrewarding path. An erroneous conjecture should not be used to reject the subject matter of the subject application.

Regarding Office Action (dated 05/06/04).Paragraph 14, the rejection has been avoided by amendment and the reasons for traversing the rejection set forth in paragraph 13 are adopted in traversing this rejection.

Regarding Office Action (dated 05/06/04) Paragraph 15, the rejection has been avoided by amendment. Scientific caution should not be exalted to definitional status. The term "usually" should not be read as expanding what is clearly stated in other parts of the specification, that the subject compounds bind to the internalizing sequence that is at other

than the ligand binding site. As discussed previously, antibodies are specifically excluded with the newly submitted amendments.

Regarding Office Action (dated 05/06/04) Paragraph 16, this reference has been discussed in relation to the foreign analog of the subject U.S. patent. For the same reasons as set forth in paragraph 13, the rejection is in part avoided and in part traversed.

Regarding Office Action (dated 05/06/04) Paragraph 17, this reference has been discussed in relation to the foreign analog of the subject U.S. patent. For the same reasons as set forth in paragraph 13, the rejection is in part avoided and in part traversed.

Regarding Office Action (dated 05/06/04) Paragraph 18, until there is some indication of allowance of claims, a terminal disclaimer is submitted to be premature.

Regarding Office Action (dated 05/06/04) Paragraph 19, until there is some indication of allowance of claims, a terminal disclaimer is submitted to be premature.

Regarding Office Action (dated 05/06/04) Paragraph 21, until there is some indication of allowance of claims, a showing that there is a common assignee at the time of the invention is premature. The Examiner is requested to indicate what would suffice to provide such a showing as both applications are assigned to the same assignee, Receptron, Inc. as a matter of record and the inventorship is common.

Regarding Office Action (dated 05/06/04) Paragraph 22, Applicants' attorney apologizes for the incorrect citation, which should be stricken from the IDS.

The Examiner's meticulous consideration of the application is appreciated. This invention is a very important asset of the subject assignee and the assignee wishes to ensure that any claims that are issued have been thoroughly considered.

In view of the above amendments and remarks, the Examiner is respectfully requested to withdraw the rejections and all the pending claims, subject to resolution of the double patenting rejections. If the Examiner believes that the prosecution of the subject application may be expedited by a telephonic interview, the Examiner is hereby authorized to call Bertram Rowland collect at (650) 344-4674.

Respectfully submitted,

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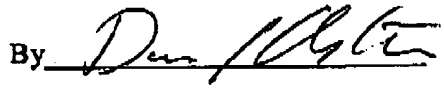
SCHMITT & ASTON, LLP

By 

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